ACS Sustainable Chemistry & Engineering

Research Article

pubs.acs.org/journal/ascecg

A Three-Component Catalyst-Free Approach to Regioselective Synthesis of Dual Highly Functionalized Fused Pyrrole Derivatives in Water−Ethanol Media: Thermodynamics versus Kinetics

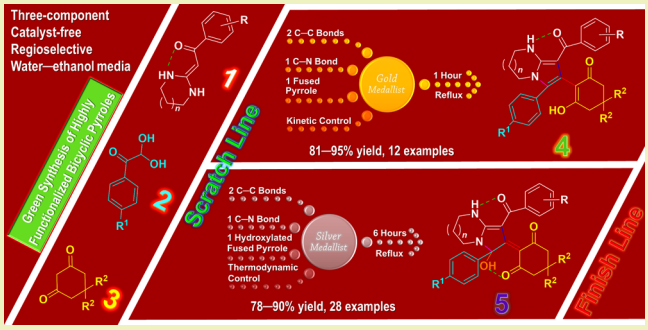
Xue-Bing Chen,[†] Zhi-Cheng Liu,[†] Li-Fen Yang,[†] Sheng-Jiao Yan,*[,†] and Jun Lin*[,†,‡]

[†]Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, P. R. China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Supporting Information

ABSTRACT: A three-component catalyst-free protocol for the regioselective synthesis of dual highly functionalized fused pyrroles has been developed from a cascade [3 + 2] cyclization of heterocyclic ketene aminals (HKAs) **1** with arylglyoxal monohydrates **2** and cyclohexane-1,3-diones **3** in water−ethanol media. The kinetically controlled products **4** could be synthesized within 1 h but would irreversibly transform to thermodynamically controlled products **5** over an additional 5 h. At the same time, the transformative synthesis of **5a** from **4a** by controlling the oxygen or nitrogen proved the proposed mechanism. Furthermore, the DFT calculation also corroborated that the stability of products **5** are a 100,000 times more thermodynamically stable than products **4**. Finally, the origin of the greater stability of **5** could be explained by the reduced density gradient (RDG) analysis, which hinted that the crucial factors are the formation of a new intramolecular hydrogen bond and the release of the steric effect of the crowded rings. In conclusion, this novel synthetic strategy offers an alternative method using thermodynamic or kinetic control for regioselective construction of biologically meaningful fused pyrrole architectures from a concise, rapid, and environmentally friendly vision.



KEYWORDS: *Green and sustainable chemistry, Multicomponent reactions, Catalyst-free, Water−ethanol media, Regioselective synthesis, Fused pyrroles, Heterocyclic ketene aminals, Thermodynamic, Kinetic*

INTRODUCTION

Green chemistry or sustainable chemistry is defined by the U.S. Environmental Protection Agency (EPA) as "the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances".[1−3] In recent years, the most pivotal area in green synthesis has been fostered by the search for environmentally benign reaction media to replace commonly used organic solvents in chemical processes[4−6] or designing one-pot reactions to construct diverse molecular libraries.[7,8] Toward fulfilling these goals, multicomponent reactions (MCRs)[9−14] can be recognized as one of the most direct, effective, and rapid methods for greener organic synthesis.

MCRs are synthetically useful and unique organic reactions where at least three polyfunctional raw materials combine and react in an ordered fashion to give a final product via a one-pot procedure. With its inherent characteristics,[15] i.e., chemo- and regioselectivity, atom economy, step efficiency, diversity, and operational simplicity, etc. in an eco-compatible chemistry, it has therefore become an essential tool for generating complex molecular libraries in the screening of potential biologically and pharmacologically active candidates. However, developing novel MCRs with advantages both from the perspective of sustainable chemistry and synthetic chemistry is still in a burgeoning phase.

Pyrroles are simple heterocycles that are frequently found in a broad range of natural products and pharmaceuticals;[16−18] in particular, polysubstituted fused pyrroles (PSFPs) are of great interest not only for the inauguration of novel synthetic methodologies but also for developing reagents for medical treatment. It has been demonstrated that PSFPs possess wide-spectrum pharmacological activities (Figure 1), including inhibition of enzymes[19−23] and receptors[24−26] as well as antiviral,[27,28] antibacterial,[29] antitumor,[30−33] anti-inflammatory,[34] antiprotozoal,[35] antimicrobial,[36] and antifungal activities.[37]

To date, several approaches have been explored for the construction of pyrrole derivatives based on the MCRs.[38] There are a few reported methods[39−46] that meet the principles of green chemistry, but the majority are accompanied by

Received: December 13, 2013
Revised: April 1, 2014
Published: April 7, 2014

 © 2014 American Chemical Society

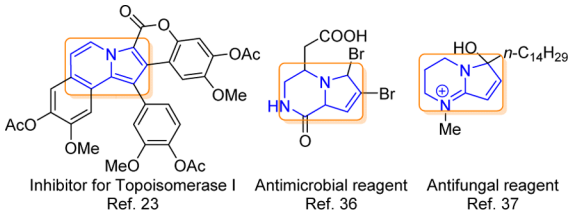


Figure 1. Polysubstituted fused pyrroles (PSFPs) as reagents for medical treatment.

shortcomings, viz., stoichiometric catalysts, precious metals, and toxic solvents. Unquestionably, the outcome of these unsustainable procedures produces large amounts of waste and greatly restricts practical applications.

As a group of versatile and powerful building blocks, heterocyclic ketene aminals (HKAs)[47−49] have been widely used for concise access to many pharmacologically interesting heterocyclic and fused heterocyclic compounds by employing MCRs.[50−54] Compared with classical enaminones,[55−58] unique structural features, such as the highly polarized C=C bond, gem-diamino group, intramolecular hydrogen bond, and their additional aromatic substituent endow HKAs with special meaning for chemo-, regio-, and stereoselective construction of biologically active fused heterocycles in a sustainable manner. So far, a number of new natural product-like heterocycles have been successfully developed based on HKAs, but even so, their synthetic methodology and its associated medicinal activity relationship should engage the attention of the chemistry community.

To the best of our knowledge, the multicomponent synthesis of *N*-bridgeheaded fused pyrroles via a catalyst-free tandem reaction in water−ethanol media has not been explored. For the purpose of continuing our previous endeavors in the fabrication of aza heterocycles,[59−64] we propose here a [3 + 2] cyclization reaction of 1,3-bidonors **1** (HKAs) with 1,2-biacceptors **2** (arylglyoxal monohydrates) and monodonors **3** (cyclohexane-1,3-diones) for the regioselective synthesis of two types of bicyclic pyrrole derivatives **4** and **5** in high yield via a one-pot, catalyst-free, thermodynamics versus kinetics protocol (Scheme 1). This approach offers an alternative method to regioselective construction of fused pyrrole architectures with potential biological activities based on a concise, rapid, and environmentally friendly vision.

EXPERIMENTAL SECTION

Computational Methods. All calculations were performed with the Gaussian 03 program.[65] The DFT calculations of all geometries were carried out with the B3LYP functional[66−68] and the 6-311+G(d,p) basis set.[69] The default self-consistent reaction field (SCRF) polarizable continuum model (PCM) was used with water as the solvent (dielectric constant ε = 78.3553), while UFF radii were chosen as the atomic radii to define the molecular cavity. Frequency calculations were also employed to evaluate the structures as minimum points (no imaginary frequencies) in energy and to achieve the relevant zero-point and thermal corrections to the electronic energies in the liquid phase. The values of Gibbs free energies (G) are shown in kcal mol^{-1}. The grid data for reduced density gradient (RDG) analysis[70] was generated via the Multiwfn program[71] and visualized with VMD software.[72]

General Methods. All commercially available reagents were purchased from Adamas Reagent Co., Ltd. and used without further purification unless otherwise stated. Melting points were determined on a XT-4A melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or a DRX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) with $CDCl_3$ and DMSO-d_6 as the solvents. The chemical shifts (δ) are expressed in parts per million relative to the residual deuterated solvent signal, and coupling constants (J) are given in Hertz. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellets. HRMS (ESI) was performed on an Agilent LC/Msd TOF instrument, and the data were obtained in the electron impact (EI) mode at 70 eV.

Noncommercially Available Compounds. Synthesis of HKAs **1**. This series of compounds was prepared according to a procedure described in the literature.[50] The identity of the materials was confirmed by ^{1}H and ^{13}C NMR and by their MS spectra.

General Procedure for the Synthesis of Compounds 4. HKAs **1** (1 mmol), arylglyoxal monohydrates **2** (1.1 mmol), and cyclohexane-1,3-diones **3** (1.1 mmol) were dissolved in the mixed solvent H_2O/EtOH (16 mL, 3:1, v/v), and then the mixture was refluxed in a round-bottomed flask (25 mL). After the HKAs **1** was completely consumed (about 1 h) as indicated by TLC, a yellow precipitate formed. Subsequently, the resulting mixture was cooled to room temperature and filtered through a Buchner funnel. The precipitate was washed successively with a small amount of cold ethanol (about 5 mL) to afford the pure products **4**.

General Procedure for the Synthesis of Compounds 5. HKAs **1** (1 mmol), arylglyoxal monohydrates **2** (1.1 mmol), and cyclohexane-1,3-diones **3** (1.1 mmol) were dissolved in the mixed solvent H_2O/EtOH (16 mL, 3:1, v/v), and then the mixture was refluxed in a round-bottomed flask (25 mL). After the HKAs **1** was completely consumed (about 6 h) as indicated by TLC, a yellow solution formed. Then, the resulting solution was cooled to room temperature and diluted with water (50 mL). Afterward, the mixture was extracted with EtOAc (50 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The pure products **5** were isolated by flash column chromatography of the residue obtained by evaporation of the filtrate on silica gel (200−300 mesh) with petroleum ether−EtOAc (1:2, v/v) as the eluent.

General Procedure for the Transformative Synthesis of Compounds 5 from 4. **4** (1 mmol) was dissolved in the mixed solvent H_2O/EtOH (16 mL, 3:1, v/v), and then the mixture was refluxed in a round-bottomed flask (25 mL). After **4** was completely consumed (about 24 h) as indicated by TLC, a yellow solution formed. Then, the resulting solution was cooled to room temperature and diluted with water (50 mL). Afterward, the mixture was extracted with EtOAc (50 mL × 2). The combined organic extracts were dried

Scheme 1. General Strategy for Cascade Synthesis of Target Compounds 4 and 5

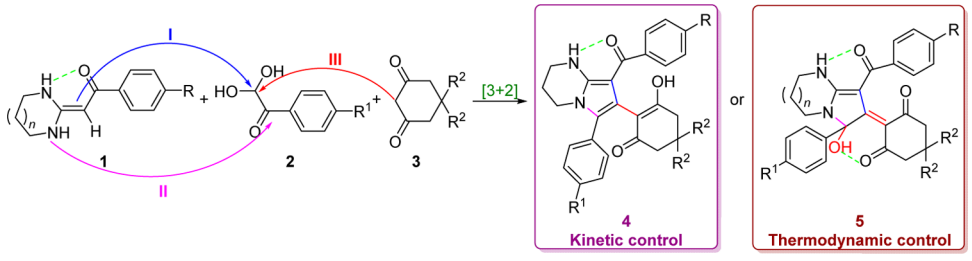
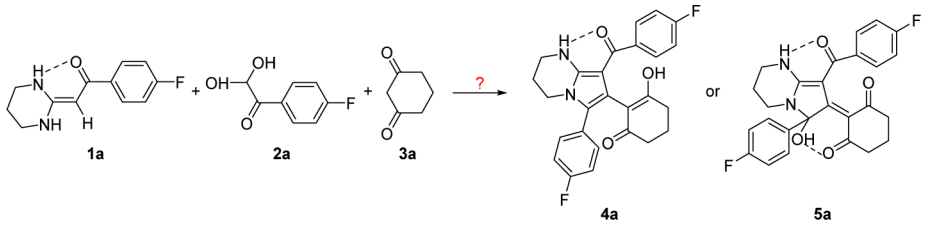


Table 1. Screening Optimum Reaction Conditions[a]



entry	solvent	catalyst	T (°C)	t (h)	yield[b] (%) 4a	yield[b] (%) 5a
1	EtOH	–	r.t.	6	trace	N.R.
2	EtOH	–	reflux	1	90	trace
3	EtOH	–	reflux	6	N.R.	84
4	EtOH	Et_3N	reflux	1	81	5
5	EtOH	Et_3N	reflux	6	2	74
6	EtOH	K_2CO_3	reflux	1	14	2
7	EtOH	K_2CO_3	reflux	6	N.R.	44
8	EtOH	HOAc	reflux	1	20	45
9	EtOH	HOAc	reflux	6	N.R.	52
10	CH_3CN	–	reflux	6	N.R.	56
11	CH_3CN	Et_3N	reflux	6	N.R.	57
12	CH_3CN	K_2CO_3	reflux	6	N.R.	47
13	CH_3CN	HOAc	reflux	6	N.R.	53
14	1,4-dioxane	–	reflux	6	N.R.	89
15	1,4-dioxane	Et_3N	reflux	6	N.R.	89
16	1,4-dioxane	K_2CO_3	reflux	6	N.R.	83
17	1,4-dioxane	HOAc	reflux	6	N.R.	85
18	THF	–	reflux	6	N.R.	84
19	THF	Et_3N	reflux	6	N.R.	85
20	THF	K_2CO_3	reflux	6	N.R.	85
21	THF	HOAc	reflux	6	N.R.	79
22	H_2O	–	reflux	24	N.R.	N.R.
23	H_2O	Et_3N	reflux	24	12	N.R.
24	H_2O	K_2CO_3	reflux	24	N.R.	5
25	H_2O	HOAc	reflux	24	trace	14
26	H_2O/EtOH (2:1, v-v)	–	reflux	1	91	trace
27	H_2O/EtOH (2:1, v-v)	–	reflux	6	trace	84
28	H_2O/EtOH (3:1, v-v)	–	reflux	1	93	trace
29	H_2O/EtOH (3:1, v-v)	–	reflux	6	trace	87

[a]Reactions (entries 1–13) were carried out using **1a** (1.0 mmol), **2a** (1.1 mmol), **3a** (1.1 mmol), and solvent (16 mL). [b]Isolated yield based on HKA **1a**, N.R. = no reaction.

over anhydrous Na_2SO_4 and evaporated in vacuo. The pure products **5** were isolated by flash column chromatography of the residue obtained by evaporation of the filtrate on silica gel (200–300 mesh) with petroleum ether–EtOAc (1:2, v/v) as the eluent.

RESULTS AND DISCUSSION

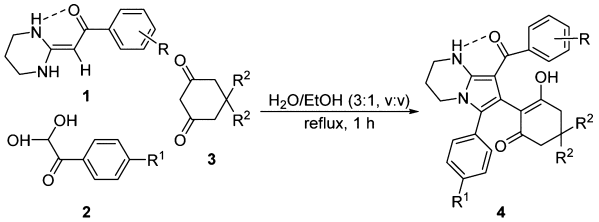
Initially, the reaction of HKA (**1a**) with 1-(4-fluorophenyl)-2,2-dihydroxyethan-1-one (**2a**) and cyclohexane-1,3-dione (**3a**) was chosen as a model for screening optimum reaction conditions (Table 1). The screening began by evaluating the reaction in the absence of any catalyst in anhydrous ethanol at room temperature; no transformation occurred within 6 h (Table 1, entry 1). Nevertheless, when the reaction was performed at reflux for 1 h, compound **4a** precipitated from the solvent and was obtained in 90% yield (Table 1, entry 2). Thereafter, we tried to completely consume the starting materials, which prolonged the time of the reaction by many hours; yet a surprising result came about, i.e., compound **4a** gradually transformed to **5a** with a yield of 84% (Table 1, entry 3). In order to efficiently obtain a sort of unitary final product, other attempts were also made. For instance, three kinds of catalyst (basic and acidic), i.e., Et_3N, K_2CO_3, and HAc, were individually added to the original mixture (Table 1, entries 4–9). However, the yields of **4a** and **5a** were sacrificed, and likewise, the vying preference for the formation of **4a** or **5a** was unsatisfied. Obviously, the presence of catalysts could not efficiently promote the reaction in a chemoselective or regioselective way. Subsequently, several aprotic solvents (CH_3CN, 1,4-dioxane, and THF) were employed as reaction media (Table 1, entries 10–21). Unluckily, because of the excellent solubility of the **4a**, the corresponding target material could not be separated from the mother liquid. Thus, the use of an aprotic solvent offered a good medium for selectively obtaining the product **5a**. Of course, a greener solvent water was also considered. Unfortunately, the yields of products **4a** and **5a** were not ideal even under catalytic conditions (Table 1, entries 22–25). Interestingly, when anhydrous ethanol was diluted with two or three portions of water (Table 1, entries

dx.doi.org/10.1021/sc500170d | ACS Sustainable Chem. Eng. 2014, 2, 1155–1163

26−29), and especially when the volume ratio of H_2O/EtOH was changed to 3:1 as a mixed solvent, the yields of **4a** and **5a** were increased to 93% and 87%, respectively (Table 1, entries 28 and 29). Therefore, it can be concluded that the optimum reaction conditions for the preparation of **4a** or **5a** were catalyst-free, H_2O/EtOH (3:1, v:v) as the medium, and reflux for 1 or 6 h.

Having established the optimum reaction conditions, the substrate scope of our protocol was tested. The results are presented in Tables 2 and 3. In general, the synthesis of

Table 2. One-Pot Protocol for Regioselective Synthesis of Fused Pyrrole Derivatives 4[a]



1 2 3 4

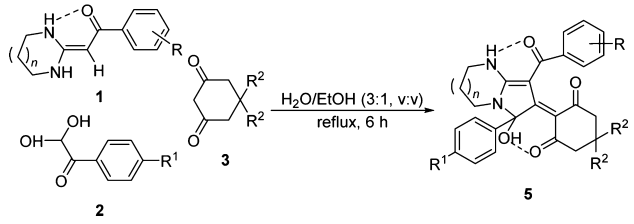
entry	1 (R)	2 (R^1)	3 (R^2)	4	yield[b] (%)
1	**1a** (*p*-F)	**2a** (F)	**3a** (H)	**4a**	93
2	**1a** (*p*-F)	**2b** (H)	**3a** (H)	**4b**	91
3	**1a** (*p*-F)	**2b** (H)	**3b** (CH_3)	**4c**	87
4	**1b** (*o*-F)	**2a** (F)	**3a** (H)	**4d**	95
5	**1b** (*o*-F)	**2b** (H)	**3a** (H)	**4e**	95
6	**1b** (*o*-F)	**2a** (F)	**3b** (CH_3)	**4f**	90
7	**1b** (*o*-F)	**2b** (H)	**3b** (CH_3)	**4g**	83
8	**1c** (*o*-Cl)	**2a** (F)	**3a** (H)	**4h**	93
9	**1c** (*o*-Cl)	**2b** (H)	**3a** (H)	**4i**	92
10	**1c** (*o*-Cl)	**2a** (F)	**3b** (CH_3)	**4j**	85
11	**1c** (*o*-Cl)	**2b** (H)	**3b** (CH_3)	**4k**	81
12	**1d** (*p*-H)	**2a** (F)	**3a** (H)	**4l**	81

[a]All reactions were run under the following conditions: **1** (1.0 mmol), **2** (1.1 mmol), and **3** (1.1 mmol) were dissolved in the mixed solvent H_2O/EtOH (16 mL, 3:1, v/v), and then the reaction was carried out under reflux for 1 h. [b]Isolated yield based on HKAs **1**.

compounds **4** was rapidly finished within 1 h in all cases, but the final products **4** could only be synthesized from HKAs **1** that contained substituents (R) of *ortho*-fluoro, *ortho*-chloro, and *para*-fluoro. The main reason was the excellent solubility of the products when R was substituted with methyl, methoxyl, or hydrogen, which made it difficult to separate out solids even in an ice bath. Hence, it was necessary to purify these products by column chromatography or recrystallization. Unfortunately, compounds **4** were all converted to compounds **5** during the course of purification. Hitherto, a small library of fused pyrroles was readily achieved in one-pot via a kinetically controlled reaction (Table 2).

Having completed the synthesis of compounds **4**, we turned our attention to investigating the three-component domino reaction for preparing the other target materials **5**. In the beginning, the substrate scope of **2** and **3** were tested. The results showed that the reaction is tolerated when **2** bear an electron-withdrawing group (R^1 = F) and **3** have a gem-dimethyl group (R^2 = CH_3) (e.g., Table 3, entries 1−4). It was also observed that the substituents (R^1 and R^2) on substrates **2** and **3** had some influence on the yields of **5**. That is, the R^1 group, which was substituted by fluorine (R^1 = F), afforded higher yields than those with no substitutions (R^1 = H) (e.g.,

Table 3. One-Pot Protocol for Regioselective Synthesis of Hydroxylated Fused Pyrrole Derivatives 5[a]



1 2 3 5

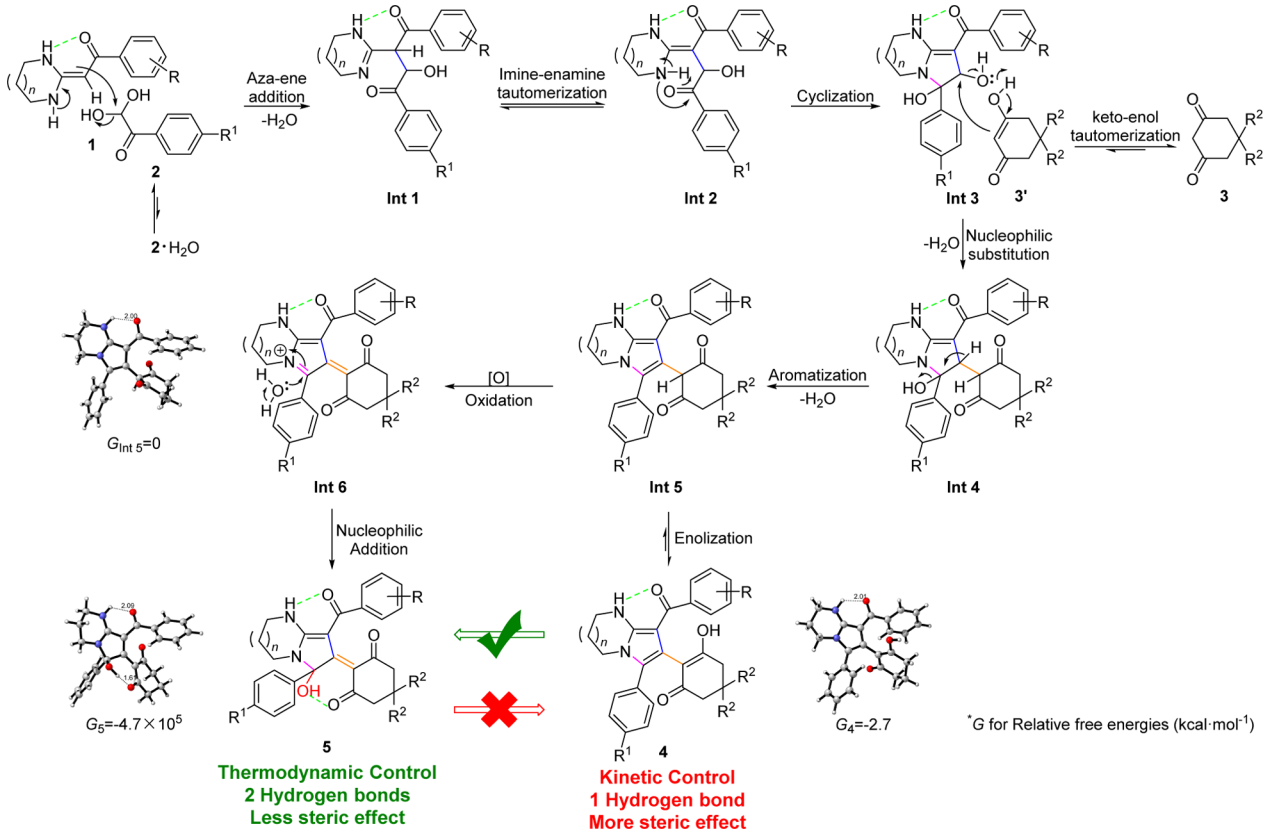
entry	1[b] (R)	2 (R^1)	3 (R^2)	5	yield[c] (%)
1	**1a** (*p*-F)	**2a** (F)	**3a** (H)	**5a**	87
2	**1a** (*p*-F)	**2b** (H)	**3a** (H)	**5b**	86
3	**1a** (*p*-F)	**2a** (F)	**3b** (CH_3)	**5c**	83
4	**1a** (*p*-F)	**2b** (H)	**3b** (CH_3)	**5d**	81
5	**1b** (*o*-F)	**2a** (F)	**3a** (H)	**5e**	90
6	**1b** (*o*-F)	**2b** (H)	**3a** (H)	**5f**	90
7	**1b** (*o*-F)	**2a** (F)	**3b** (CH_3)	**5g**	84
8	**1b** (*o*-F)	**2b** (H)	**3b** (CH_3)	**5h**	82
9	**1c** (*p*-Cl)	**2a** (F)	**3a** (H)	**5i**	85
10	**1c** (*p*-Cl)	**2b** (H)	**3a** (H)	**5j**	85
11	**1c** (*p*-Cl)	**2a** (F)	**3b** (CH_3)	**5k**	81
12	**1c** (*p*-Cl)	**2b** (H)	**3b** (CH_3)	**5l**	79
13	**1d** (*o*-Cl)	**2b** (H)	**3a** (H)	**5m**	83
14	**1d** (*o*-Cl)	**2a** (F)	**3b** (CH_3)	**5n**	80
15	**1d** (*o*-Cl)	**2b** (H)	**3b** (CH_3)	**5o**	79
16	**1e** (*p*-H)	**2a** (F)	**3a** (H)	**5p**	85
17	**1e** (*p*-H)	**2b** (H)	**3a** (H)	**5q**	85
18	**1e** (*p*-H)	**2a** (F)	**3b** (CH_3)	**5r**	81
19	**1e** (*p*-H)	**2b** (H)	**3b** (CH_3)	**5s**	82
20	**1f** (*p*-CH_3)	**2a** (F)	**3a** (H)	**5t**	84
21	**1f** (*p*-CH_3)	**2b** (H)	**3a** (H)	**5u**	81
22	**1f** (*p*-CH_3)	**2a** (F)	**3b** (CH_3)	**5v**	81
23	**1f** (*p*-CH_3)	**2b** (H)	**3b** (CH_3)	**5w**	79
24	**1g** (*p*-OCH_3)	**2a** (F)	**3a** (H)	**5x**	82
25	**1g** (*p*-OCH_3)	**2b** (H)	**3a** (H)	**5y**	79
26	**1g** (*p*-OCH_3)	**2a** (F)	**3b** (CH_3)	**5z**	80
27	**1g** (*p*-OCH_3)	**2b** (H)	**3b** (CH_3)	**5a′**	78
28	**1h** (*p*-CH_3)	**2b** (H)	**3a** (H)	**5a″**	85

[a]All reactions were run under the following conditions: **1** (1.0 mmol), **2** (1.1 mmol), and **3** (1.1 mmol) were dissolved in the mixed solvent H_2O/EtOH (16 mL, 3:1, v/v), and then the reaction was carried out under reflux for 6 h. [b]For HKA **1h**, n = 2; for the others, n = 1. [c]Isolated yield based on HKAs **1**.

Table 3, entries 1 and 2), and the R^2 groups, which were substituted by methyl (R^2 = CH_3), gave lower yields (e.g., Table 3, entries 1 and 3). Next, the scope of the reaction was also extended by using other HKAs **1**. Evidently, the electronic nature of the aromatic rings of **1** significantly impacted the yield of the reaction. Namely, the R group, which was an electron-withdrawing group (e.g., R = F or Cl), could encourage the yields of **5** (e.g., Table 3, entries 1, 9, 20, and 24). In addition, HKAs with substituents at the *ortho*-position afforded higher yields than their counterparts at the *para*-position (e.g., Table 3, entries 1 and 5). Furthermore, the seven-membered HKA **1h** was also employed and gave product **5a″** with higher yield than the corresponding six-membered product **5t** (Table 3, entries 20 and 28). Overall, the hydroxylated fused pyrroles **5** were slowly formed in one-pot via a thermodynamically controlled reaction (Table 3).

The chemical structures of target compounds **4** and **5** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS

Scheme 2. Mechanism Hypotheses for Synthesis of Target Compounds 4 and 5

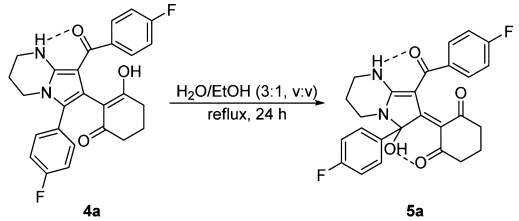


spectroscopy, while products **4l** and **5a** were unequivocally confirmed by X-ray diffraction analysis of two selected single crystals (CCDC 968949 and 961278) (Figures S81 and S82, Supporting Information).

The mechanism hypotheses for the dual regioselective reactions are proposed and illustrated in Scheme 2. The HKA **1**, with a strong electron-withdrawing keto-carbonyl group at the α-position and an electron-donating gem-diamino group on the diazaheterocycle, can serve as a heteroene component reacting with the tertiary carbon of **2** from **Int 1** via an aza−ene reaction[73] accompanying the creation of a C−C bond. Thereafter, **Int 1** tautomerizes to **Int 2** by an imine−enamine process,[74] and then the NH group attacks the intramolecular carbonyl group to afford **Int 3**. Subsequently, **Int 4** is generated through the addition of **3′** to **Int 3** and the elimination of one water molecule. Hitherto, two C−C bonds and one C−N bond are formed. Afterward, aromatization occurs and provides **Int 5**. As a road sign, the **Int 5** not only rapidly transform into one of the target materials **4** (**Int 5** → **4**) via the enolization but also slowly translate to the other hydroxylated target materials **5** (**Int 5** → **5**) via a tandem sequence, i.e., the oxidation of **Int 5** and the nucleophilic addition of one water molecule to **Int 6**. On the basis of these mechanistic deductions, we can anticipate that target compounds **4** and **5** are the kinetically and thermodynamically controlled results, respectively.

For the sake of proving the proposed mechanism and explaining the relatively high stability of the thermodynamically favored compounds **5**, product **4a** was chosen as the representative and refluxed for 24 h in the same medium (H_2O:EtOH, 3:1, v/v). To our delight, the transformation of compound **4a** to **5a** was successful (Table 4, entry 1).

Table 4. Transformative Synthesis of 5a from 4a[a]



entry	*p* (atm)	yield (%)
1	air (1)	95
2	N_2 (1)	N.R.
3	O_2 (1)	97

[a]All reactions were run under the following conditions: **4a** (1.0 mmol) was dissolved in the mixed solvent H_2O/EtOH (16 mL, 3:1, v/v), and then the reaction was carried out under reflux for 24 h. [b]N.R. = no reaction.

Contrasting the ^{13}C NMR spectra (Figure 2) between **4a** and **5a** revealed that once the transformation occurred, the chemical shifts of C3 and C5 move to the low field region and, on the contrary, C4 moves to the high field region. This alteration in characteristic peaks could be explained by mesomeric effects: (i) The newly generated π-acceptor (C═O) causes a low-field shift in both the C3 and C5 positions. (ii) The novel σ-donor (OH) leads to C4 being better shielded; hence, the resonance signal lies in a higher field.

Additionally, the transformative synthesis of **5a** from **4a** under pure oxygen or nitrogen atmospheres was also performed (Table 4, entries 2 and 3). The process was obviously accelerated under oxygen atmosphere and grievously decel-

dx.doi.org/10.1021/sc500170d | ACS Sustainable Chem. Eng. 2014, 2, 1155−1163

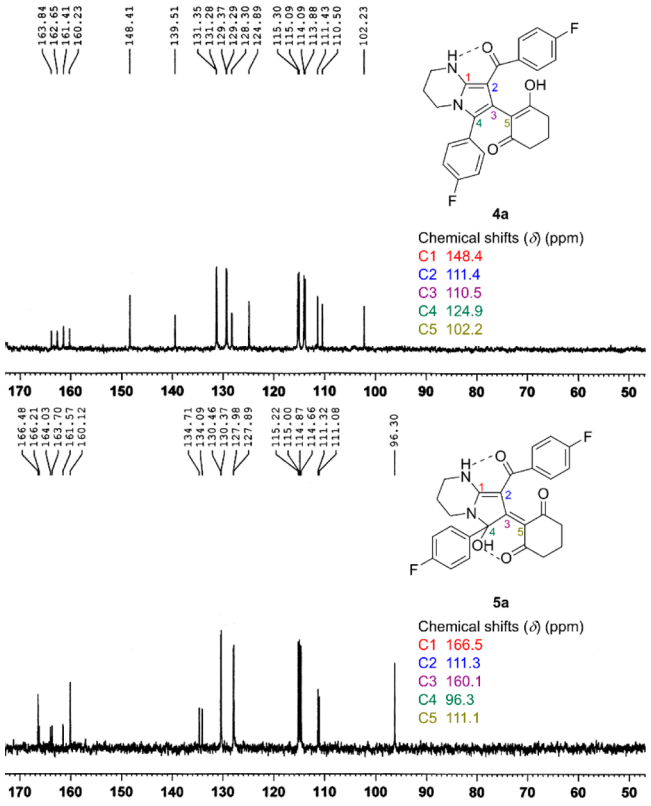


Figure 2. ^{13}C NMR spectra (100 MHz) of compounds **4a** and **5a**.

erated under nitrogen atmosphere. The absence of oxygen caused the synthesis of **5a** to fail. Accordingly, the combined experimental results presented above were highly convergent with the mechanism depicted in Scheme 2. Distinctively, it answers the questions from a macroscopic view, i.e., why did the transformation of **4** to **5** occur after the formation of **4**, and where did the oxidation take place? On the other hand, we can propose that the transformative reaction of **4** to **5** (Scheme 2, **4** → **Int 5** → **5**) is the most difficult, and then the irreversible transformation (Scheme 2, **Int 5** → **5**) yielding, at last, the synthesis of **4** is the easiest (Scheme 2, **Int 5** → **4**).

Simultaneously, to evaluate the likelihood that the transformation occurred, we carried out calculations of the possible configurations and the sum of electronic and thermal free energy (G) of **4**, **Int 5**, and **5**. We found that the most stable configuration of **4** was a 100,000 times higher in thermodynamics than the most stable configuration of **5**, and the most stable configuration of **Int 5** was close to **4** ($G_5 \ll G_4 \approx G_{\text{Int 5}}$). Therefore, this result suggests that **4** could be easily transformed to more stable products **5**. Of course, analysis of the types of changes in weak interactions occurring here could provide valuable information to further explain the origin of the greater stability of the thermodynamically controlled species **5**. Therefore, we depicted the RDG isosurface of the model compounds **4** and **5** in Figure 3. It can observed that when the transformation is completed that the following occur: (i) The weak hydrogen bond (N−H···O) keeps the same pattern. (ii) The weak steric effect between rings **A** and **C** turns into a van der Waals interaction. (iii) The novel hydroxyl donates a strong hydrogen bond (O−H···O) between rings **B** and **E**. (iv) The steric effect among rings **C**, **D**, and **E** moves to the periphery of the molecular skeleton, and as a result, the greater stability of **5** mainly rests on the formation of a new intramolecular hydrogen bond as well as the dispersion and release of the steric effect among the crowded rings **C**, **D**, and **E**.

CONCLUSIONS

In summary, we have successfully developed a new three-component catalyst-free reaction for the regioselective synthesis of two libraries of highly functionalized bicyclic pyrrole derivatives via a [3 + 2] cyclization of HKAs **1** with arylglyoxal monohydrates **2** and cyclohexane-1,3-diones **3** in water−ethanol media. This is the first example of the thermodynamically versus kinetically controlled preparation of fused pyrrole derivatives. The reaction was shown to have attractive features, including environmentally friendly conditions, excellent regioselectivity, and molecular diversities. Moreover, these series of bicyclic pyrroles may provide potential biological activities for medical treatment. Our further investigations into the in vitro biological activities of compounds **4** and **5** as well as in-depth computations to interpret the competition between thermody-

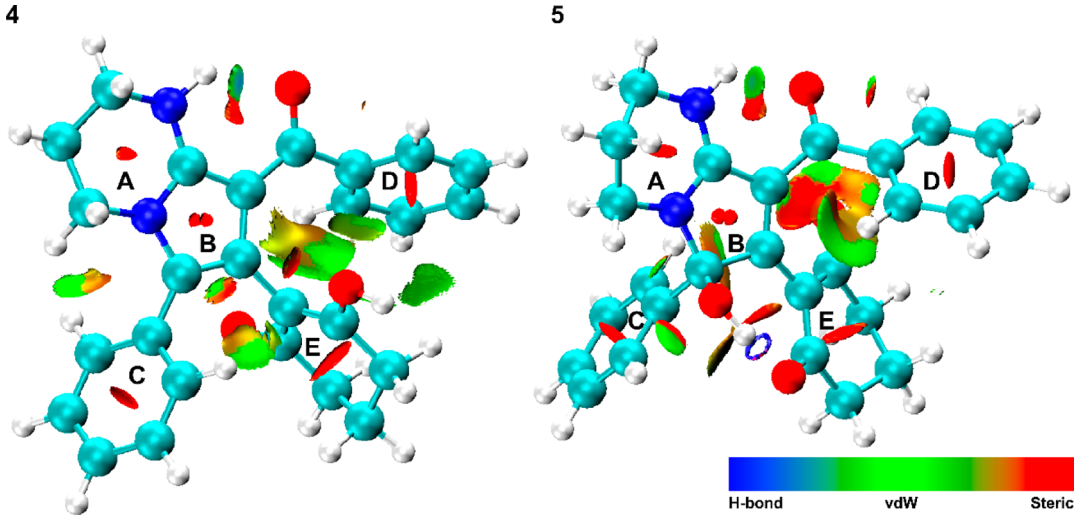


Figure 3. Reduced density gradient isosurface of model compounds **4** and **5**. The color presented in the scale bar denotes the type of weak interaction (blue = hydrogen bond, green = van der Waals interaction, brown = weak steric effect, and red = strong steric effect).

dx.doi.org/10.1021/sc500170d | ACS Sustainable Chem. Eng. 2014, 2, 1155−1163

namics and kinetics by seeking possible energy profiles of the dual reaction are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic and analytical data, as well as the original copy of ^{1}H and ^{13}C NMR spectra of all new compounds. Computed thermodynamic data and Cartesian coordinates. Crystal X-ray structures (CCDC 968949 and 961278) of compounds **4l** and **5b**. X-ray crystallographic data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yansj@ynu.edu.cn (S.-J.Y.). Tel and Fax: +86 871 65033215.

*E-mail: linjun@ynu.edu.cn (J.L.). Tel and Fax: +86 871 65033215.

Author Contributions

X.-B. Chen and Z.-C. Liu contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Program for Changjiang Scholars and Innovative Research Team in University (IRT13095), National Natural Science Foundation of China (81160384, 21162037, 21262042, U1202221, and 21362042), Reserve Talent Foundation of Yunnan Province for Middle-aged and Young Academic and Technical Leaders (2012HB001), and Scholarship Award for Excellent Doctoral Student of Yunnan Province. We also thank Prof. Dr. Wen-Wen Qu of Kunming University of Science and Technology for her helpful discussion and suggestions.

■ REFERENCES

(1) U.S. Environmental Protection Agency. http://www.epa.gov (accessed March 1, 2014).

(2) Dunn, P. J. The importance of green chemistry in process research and development. *Chem. Soc. Rev.* **2012**, *41*, 1452−1461.

(3) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007; p 1.

(4) Kerton, F. M.; Marriott, R. *Alternative Solvents for Green Chemistry*, 2nd ed.; RSC Publishing: Cambridge, U.K., 2013; pp 1−3.

(5) Simon, M.-O.; Li, C.-J. Green chemistry oriented organic synthesis in water. *Chem. Soc. Rev.* **2012**, *41*, 1415−1427.

(6) Orha, L.; Akien, G. R.; Horváth, I. T. In *Handbook of Green Chemistry, Vol. 7: Green Synthesis*; Li, C.-J., Ed.; Wiley-VCH: Weinheim, Germany, 2012; p 117.

(7) Wyatt, P.; Warren, S. *Organic Synthesis: Strategy and Control*; John Wiley & Sons Ltd: Chichester, U.K., 2007; pp 864−865.

(8) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006; p 5.

(9) Eckert, H. Diversity oriented syntheses of conventional heterocycles by smart multi component reactions (MCRs) of the last decade. *Molecules* **2012**, *17*, 1074−1102.

(10) Ramachary, D. B.; Jain, S. Sequential one-pot combination of multi-component and multi-catalysis cascade reactions: an emerging technology in organic synthesis. *Org. Biomol. Chem.* **2011**, *9*, 1277−1300.

(11) Kumaravel, K.; Vasuki, G. Multi-component reactions in water. *Curr. Org. Chem.* **2009**, *13*, 1820−1841.

(12) Syamala, M. Recent progress in three-component reactions: An update. *Org. Prep. Proced. Int.* **2009**, *41*, 1−68.

(13) Doble, M.; Kruthiventi, A. K. *Green Chemistry and Processes*; Elsevier: Oxford, U.K., 2007; pp 35−37.

(14) Hulme, C. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 311−312.

(15) Zhu, J.; Wang, Q.; Wang, M.-X. In *Handbook of Green Chemistry, Vol. 7: Green Synthesis*; Li, C.-J., Ed.; Wiley-VCH: Weinheim, Germany, 2012; pp 121−122.

(16) Mal, D.; Shome, B.; Dinda, B. K. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 187−192.

(17) Liddell, J. R. Pyrrolizidine alkaloids. *Nat. Prod. Rep.* **2002**, *19*, 773−781.

(18) O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **2000**, *17*, 435−446.

(19) Liu, Y.; Fang, J.-P.; Cai, H.-Y.; Xiao, F.; Ding, K.; Hua, Y.-H. Identification and synthesis of substituted pyrrolo[2,3-*d*]pyrimidines as novel firefly luciferase inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 5473−5482.

(20) Weinberg, L. R.; Albom, M. S.; Angeles, T. S.; Breslin, H. J.; Gingrich, D. E.; Huang, Z.-Q.; Lisko, J. G.; Mason, J. L.; Milkiewicz, K. L.; Thieu, T. V.; Underiner, T. L.; Wells, G. J.; Wells-Knecht, K. J.; Dorsey, B. D. 2,7-Pyrrolo[2,1-*f*][1,2,4]triazines as JAK2 inhibitors: Modification of target structure to minimize reactive metabolite formation. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7325−7330.

(21) Reddy, G. R.; Reddy, T. R.; Joseph, S. C.; Reddy, K. S.; Reddy, L. S.; Kumar, P. M.; Krishna, G. R.; Reddy, C. M.; Rambabu, D.; Kapavarapu, R.; Lakshmi, C.; Meda, T.; Priya, K. K.; Parsad, K. V. L; Pal, M. Pd-mediated new synthesis of pyrroles: Their evaluation as potential inhibitors of phosphodiesterase 4. *Chem. Commun.* **2011**, *47*, 7779−7781.

(22) Oguro, Y.; Miyamoto, N.; Okada, K.; Takagi, T.; Iwata, H.; Awazu, Y.; Miki, H.; Hori, A.; Kamiyama, K.; Imamura, S. Design, synthesis, and evaluation of 5-methyl-4-phenoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine derivatives: Novel VEGFR2 kinase inhibitors binding to inactive kinase conformation. *Bioorg. Med. Chem.* **2010**, *18*, 7260−7273.

(23) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. Molecular determinants of topoisomerase I poisoning by lamellarins: Comparison with Camptothecin and structure-activity relationships. *J. Med. Chem.* **2005**, *48*, 3796−3807.

(24) Pittalà, V.; Siracusa, M. A.; Modica, M. N.; Salerno, L.; Pedretti, A.; Vistoli, G.; Cagnotto, A.; Mennini, T.; Romeo, G. Synthesis and molecular modeling of 1*H*-pyrrolopyrimidine-2,4-dione derivatives as ligands for the α_1-adrenoceptors. *Bioorg. Med. Chem.* **2011**, *19*, 5260−5276.

(25) Bernotas, R. C.; Lenicek, S.; Antane, S.; Cole, D. C.; Harrison, B. L.; Robichaud, A. J.; Zhang, G.-M.; Smith, D.; Platt, B.; Lin, Q.; Li, P.; Coupet, J.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schechter, L. E. Novel 1-aminoethyl-3-arylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridines are potent 5-HT_6 agonists. *Bioorg. Med. Chem.* **2009**, *17*, 5153−5163.

(26) Castelhano, A. L.; McKibben, B.; Witter, D. J. Compounds Specific to Adenosine A1 Receptor and Uses thereof. U.S. Patent 6,878,716, B1, April 12, 2005.

(27) Regueiro-Ren, A.; Xue, Q.-M.; Swidorski, J. J.; Gong, Y.-F.; Mathew, M.; Parker, D. D.; Yang, Z.; Eggers, B.; D'Arienzo, C.; Sun, Y.-N.; Malinowski, J.; Gao, Q.; Wu, D.-D.; Langley, D. R.; Colonno, R. J.; Chien, C.; Grasela, D. M.; Zheng, M.; Lin, P.-F.; Meanwell, N. A.; Kadow, J. F. Inhibitors of human immunodeficiency virus type 1 (HIV-1) attachment. 12. structure−activity relationships associated with 4-fluoro-6-azaindole derivatives leading to the identification of 1-(4-benzoylpiperazin-1-yl)-2-(4-fluoro-7-[1,2,3]triazol-1-yl-1*H*-pyrrolo-[2,3-*c*]-pyridin-3-yl)ethane-1,2-dione (BMS-585248). *J. Med. Chem.* **2013**, *56*, 1656−1669.

(28) Varaprasad, C. V. N. S.; Ramasamy, S. K.; Girardet, J. L.; Gunic, E.; Lai, V.; Zhong, Z.; An, H.; Hong, Z. Synthesis of pyrrolo[2,3-*d*]pyrimidine nucleoside derivatives as potential anti-HCV agents. *Bioorg. Chem.* **2007**, *35*, 25−34.

(29) Trzoss, M.; Bensen, D. C.; Lia, X.-M.; Chen, Z.-Y.; Lam, T.; Zhang, J.-Z.; Creighton, C. J.; Cunningham, M. L.; Kwan, B.; Stidham, M.; Nelson, K.; Brown-Driver, V.; Castellano, A.; Shaw, K. J.; Lightstone, F. C.; Wong, S.-E.; Nguyen, T. B.; Finn, J.; Tari, L. W. Pyrrolopyrimidine inhibitors of DNA gyrase B (GyrB) and topoisomerase IV (ParE), part II: Development of inhibitors with broad spectrum, gram-negative antibacterial activity. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1537.
(30) Soares, M. I. L.; Brito, A. F.; Laranjo, M.; Paixão, J. A.; Botelho, M. F.; Pinho e Melo, T. M. V. D. Chiral 6,7-bis(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles with anti-breast cancer properties. *Eur. J. Med. Chem.* **2013**, *60*, 254−262.
(31) Wang, L.; Cherian, C.; Desmoulin, S. K.; Mitchell-Ryan, S.; Hou, Z.-J.; Matherly, L. H.; Gangjee, A. Synthesis and biological activity of 6-substituted pyrrolo[2,3-*d*]pyrimidine thienoyl regioisomers as inhibitors of de novo purine biosynthesis with selectivity for cellular uptake by high affinity folate receptors and the proton-coupled folate transporter over the reduced folate carrier. *J. Med. Chem.* **2012**, *55*, 1758−1770.
(32) Wang, L.; Desmoulin, S. K.; Cherian, C.; Polin, L.; White, K.; Kushner, J.; Fulterer, A.; Chang, M.-H.; Mitchell-Ryan, S.; Stout, M.; Romero, M. F.; Hou, Z.-J.; Matherly, L. H.; Gangjee, A. Synthesis, biological, and antitumor activity of a highly potent 6-substituted pyrrolo[2,3-*d*]pyrimidine thienoyl antifolate inhibitor with proton-coupled folate transporter and folate receptor selectivity over the reduced folate carrier that inhibits *β*-glycinamide ribonucleotide formyltransferase. *J. Med. Chem.* **2011**, *54*, 7150−7164.
(33) Tangeda, S. J.; Garlapati, A. Synthesis of new pyrrolo[2,3-*d*]pyrimidine derivatives and evaluation of their activities against human colon cancer cell lines. *Eur. J. Med. Chem.* **2010**, *45*, 1453−1458.
(34) Mohamed, M. S.; Kamel, R.; Fatahala, S. S. Synthesis and biological evaluation of some thio containing pyrrolo[2,3-*d*]pyrimidine derivatives for their anti-inflammatory and anti-microbial activities. *Eur. J. Med. Chem.* **2010**, *45*, 2994−3004.
(35) Kaspersen, S. J.; Sundby, E.; Charnock, C.; Hoff, B. H. Activity of 6-aryl-pyrrolo[2,3-*d*]pyrimidine-4-amines to *Tetrahymena*. *Bioorg. Chem.* **2012**, *44*, 35−41.
(36) Li, X.-C.; Babu, S.; Jacbo, M. R.; Khan, S. I.; Agarwal, A. K.; Clark, A. M. Natural product-based 6-hydroxy-2,3,4,6-tetrahydropyrrolo[1,2-*a*]pyrimidinium scaffold as a new antifungal template. *ACS Med. Chem. Lett.* **2011**, *2*, 391−395.
(37) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. Novel bromopyrrole alkaloids from the sponge *Agelas dispar*. *J. Nat. Prod.* **1998**, *61*, 122−125.
(38) Estévez, V.; Villacampa, M.; Menéndez, J. C. Multicomponent reactions for the synthesis of pyrroles. *Chem. Soc. Rev.* **2010**, *39*, 4402−4421.
(39) Li, M.; Lv, X.-L.; Wen, L.-R.; Hu, Z.-Q. Direct solvent-free regioselective construction of pyrrolo[1,2-*a*][1,10]phenanthrolines based on isocyanide-based multicomponent reactions. *Org. Lett.* **2013**, *15*, 1262−1265.
(40) Feng, X.; Wang, Q.; Lin, W.; Dou, G.-L.; Huang, Z.-B.; Shi, D.-Q. Highly efficient synthesis of polysubstituted pyrroles via four-component domino reaction. *Org. Lett.* **2013**, *15*, 2542−2545.
(41) Liu, J.-Y.; Li, Q.-Y.; Jiang, B.; Tu, S.-J. Three-component domino reactions providing rapid and efficient routes to fully substituted pyrroles. *RSC Adv.* **2013**, *3*, 5056−5068.
(42) Tu, X.-C.; Fan, W.; Jiang, B.; Wang, S.-L.; Tu, S.-J. A novel allylic substitution strategy to four-component synthesis of pyrazole-substituted fused pyrroles. *Tetrahedron* **2013**, *69*, 6100−6107.
(43) Meshram, H. M.; Babu, B. M.; Kumar, G. S.; Thakur, P. B.; Bangade, V. M. Catalyst-free four-component protocol for the synthesis of substituted pyrroles under reusable reaction media. *Tetrahedron Lett.* **2013**, *54*, 2296−2302.
(44) Lu, Q.; Song, G.-H.; Jasinski, J. P.; Keeleyc, A. C.; Zhang, W. One-pot double [3 + 2] cycloaddition for diastereoselective synthesis of tetracyclic pyrrolidine compounds. *Green Chem.* **2012**, *14*, 3010−3012.
(45) Jiang, B.; Li, Y.; Tu, M.-S.; Wang, S.-L.; Tu, S.-J.; Li, G.-G. Allylic amination and *N*-arylation-based domino reactions providing rapid three-component strategies to fused pyrroles with different substituted patterns. *J. Org. Chem.* **2012**, *77*, 7497−7505.
(46) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. Synthesis of functionalized pyrroles via catalyst- and solvent-free sequential three-component enamine−azoene annulation. *J. Org. Chem.* **2011**, *76*, 2860−2866.
(47) Wang, K.-M.; Yan, S.-J.; Lin, J. Heterocyclic ketene aminals: scaffolds for heterocycle molecular diversity. *Eur. J. Org. Chem.* **2014**, 1129−1145.
(48) Wang, M.-X.; Huang, Z.-T. Advances in heterocyclic ketene aminals. *Prog. Nat. Sci.* **2002**, *12*, 249−257.
(49) Huang, Z.-T.; Wang, M.-X. Heterocyclic ketene aminals. *Heterocycles* **1994**, *37*, 1233−1262.
(50) Chen, X.-B.; Liu, X.-M.; Huang, R.; Yan, S.-J.; Lin, J. Three-component synthesis of indanone-fused spirooxindole derivatives. *Eur. J. Org. Chem.* **2013**, 4607−4613.
(51) Wen, L.-R.; Sun, Q.-C.; Zhang, H.-L.; Li, M. A new rapid multicomponent domino heteroannulation of heterocyclic ketene aminals: Solvent-free regioselective synthesis of functionalized benzo[*g*]imidazo[1,2-*a*]quinolinediones. *Org. Biomol. Chem.* **2013**, *11*, 781−786.
(52) Yu, F.-C.; Huang, R.; Ni, H.-C.; Fan, J.; Yan, S.-J.; Lin, J. Three-component stereoselective synthesis of spirooxindole derivatives. *Green Chem.* **2013**, *15*, 453−462.
(53) Wen, L.-R.; Li, Z.-R.; Li, M.; Cao, H. Solvent-free and efficient synthesis of imidazo[1,2-*a*]pyridine derivatives via a one-pot three-component reaction. *Green Chem.* **2012**, *14*, 707−716.
(54) Yan, S.-J.; Chen, Y.-L.; Liu, L.; He, N.-Q.; Lin, J. Three-component solvent-free synthesis of highly substituted bicyclic pyridines containing a ring-junction nitrogen. *Green Chem.* **2010**, *12*, 2043−2052.
(55) Ferraz, H. M. C.; Gonçalo, E. R. S. Recent preparations and synthetic applications of enaminones. *Quim. Nova* **2007**, *30*, 957−964.
(56) Li, M.; Guo, W.-S.; Wen, L.-R.; Yang, H.-Z. Synthesis of enaminones and their utility in organic synthesis. *Chin. J. Org. Chem.* **2006**, *26*, 1192−1207.
(57) Negri, G.; Kascheres, C.; Kascheres, A. J. Recent development in preparation reactivity and biological activity of enaminoketones and enaminothiones and their utilization to prepare heterocyclic compounds. *J. Heterocycl. Chem.* **2004**, *41*, 461−491.
(58) Elassar, A.-Z. A.; El-Khair, A. A. Recent developments in the chemistry of enaminones. *Tetrahedron* **2003**, *59*, 8463−8480.
(59) Chen, X.-B.; Zhu, D.-D.; Wang, X.-Y.; Yan, S.-J.; Lin, J. Cascade reaction synthesis of multisubstituted bicyclic pyridone derivatives. *Tetrahedron* **2013**, *69*, 9224−9236.
(60) Zhang, Y.-C.; Liu, Z.-C.; Yang, R.; Zhang, J.-H.; Yan, S.-J.; Lin, J. Regioselective construction of 1,3-diazaheterocycle fused [1,2-*a*][1,8]-naphthyridine derivatives via cascade reaction of quinolines with heterocyclic ketene aminals: A joint experimental−computational approach. *Org. Biomol. Chem.* **2013**, *11*, 7276−7288.
(61) Yu, F.-C.; Yan, S.-J.; Hu, L.; Wang, Y.-C.; Lin, J. Cascade reaction of isatins with heterocyclic ketene aminals: Synthesis of imidazopyrroloquinoline derivatives. *Org. Lett.* **2011**, *13*, 4782−4785.
(62) Huang, C.; Yan, S.-J.; Zeng, X.-H.; Dai, X.-Y.; Zhang, Y.; Qing, C.; Lin, J. Biological evaluation of polyhalo 1,3-diazaheterocycle fused isoquinolin-1(2*H*)-imine derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 1172−1180.
(63) Yu, F.-C.; Yan, S.-J.; Huang, R.; Tang, Y.-J.; Lin, J. Three-component solvent-free synthesis of highly substituted tetrahydroimidazo[1,2-*a*]pyridines. *RSC Adv.* **2011**, *1*, 596−601.
(64) Yan, S.-J.; Chen, Y.-L.; Liu, L.; Tang, Y.-J.; Lin, J. Synthesis of novel tetracyclo-isocoumarins via AcOH-catalyzed cascade reaction of heterocyclic ketene aminals with 2,2-dihydroxy-2*H*-indene-1,3-dione. *Tetrahedron Lett.* **2011**, *52*, 465−467.
(65) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.;

Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, revision D.01*; Gaussian, Inc.: Wallingford, CT, 2004.

(66) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(67) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle−Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785−789.

(68) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. Results obtained with the correlation energy density functionals of Becke and Lee, Yang and Parr. *Chem. Phys. Lett.* **1989**, *157*, 200−206.

(69) Hariharan, P. C.; Pople, J. A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta* **1973**, *28*, 213−222.

(70) Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. Revealing noncovalent interactions. *J. Am. Chem. Soc.* **2010**, *132*, 6498−6506.

(71) Lu, T.; Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.* **2012**, *33*, 580−592.

(72) Humphrey, W.; Dalke, A.; Schulten, K. VMD: Visual molecular dynamics. *J. Mol. Graph.* **1996**, *14*, 33−38.

(73) Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. The aza-ene reaction of heterocyclic ketene aminals with enones: an efficient and simple synthetic route to fused di- and tri-heterocycles. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2087−2094.

(74) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. A novel one-pot reaction of heterocyclic ketene aminals: synthesis of a small library of tetrahydropyridinone-fused 1,3-diazaheterocycles. *Synlett* **2006**, 1835−1840.